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REVIEW

Proton pump inhibitors in cirrhosis: Tradition or evidence based practice?

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Abstract

Proton Pump Inhibitors (PPI) are very effective in inhibiting acid secretion and are extensively used in many acid related diseases. They are also often used in patients with cirrhosis sometimes in the absence of a specific acid related disease, with the aim of preventing peptic complications in patients with variceal or hypertensive gastropathic bleeding receiving multidrug treatment. Contradicting reports support their use in cirrhosis and evidence of their efficacy in this condition is poor. Moreover there are convincing papers suggesting that acid secretion is reduced in patients with liver cirrhosis. With regard to Helicobacter pylori (*H pylori*) infection, its prevalence in patients with cirrhosis is largely variable among different studies, and it seems that *H pylori* eradication does not prevent gastro-duodenal ulcer formation and bleeding. With regard to the prevention and treatment of oesophageal complications after banding or sclerotherapy of oesophageal varices, there is little evidence for a protective role of PPI. Moreover, due to liver metabolism of PPI, the dose of most available PPIs should be reduced in cirrhotics. In conclusion, the use of this class of drugs seems more habit related than evidence-based eventually leading to an increase in health costs.

Key words: Proton pump inhibitors; Cirrhosis; *Helicobacter pylori* ; Peptic ulcer; CYP P450

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INTRODUCTION

Proton Pump Inhibitors (PPI) are extensively used in different acid related diseases. Their efficacy in inhibiting acid secretion is well known[1-4], and the use of this class of drugs has increased worldwide. They act through inhibition of the H^+/K^+ ATPase of parietal cells producing the so called "inhibitory complex" and blocking HCl secretion[5]. They are metabolized in the liver by the CYP450 cytochrome[6].

PPI are also often used in patients with liver cirrhosis sometimes in the absence of a specific acid related disease, with the aim of preventing peptic complications in patients with variceal or hypertensive gastropathic bleeding receiving multidrug treatment.

The aim of this editorial is to revise the efficacy and safety profile of PPI in patients with liver cirrhosis.

GASTRIC ACID SECRETION AND LIVER CIRRHOSIS

The role of gastric secretion in cirrhosis is controversial. Some studies report reduced acid production[7-10] while others reported normal production[11-15]. The evaluation of 24-h acidity by gastric ph-metry in 49 patients with cirrhosis showed a marked hypoacidity in patients with cirrhosis compared to controls, mainly during the night hours[16]. This may depend on hemodynamic alterations consequent to portal hypertension and is supported by experimental studies showing reduced gastric acid secretion in animals with portal hypertension[17,18]. These observations rule out the relevance of gastric acid in the pathogenesis of ulcers in cirrhotics.

Gastrin, the gastric hormone whose secretion is regulated by intragastric pH, and that regulates the production of HCl and pepsin, is partially metabolized

Table 1 Prevalence of peptic ulcer in patients with liver cirrhosis

Investigator	Number of patients	Gastric ulcer prevalence (%)
Siringo, 1995	324	4.6
Chen, 1996	245	20.8
Tsai, 1998	130	16.1
Kirk, 1980	163	14.7
Rabinovitz, 1990	216	7.8

Table 2 Gastric and duodenal ulcer in patients with liver cirrhosis according to the severity of portal hypertension (from Wu *et al* 1995)

	Controls (n = 60)		Compensated cirrhosis (n = 60)		Decompensated cirrhosis (n = 60)		P
	n	%	n	%	n	%	
Duodenal ulcer	2	3.3	10	16.7	8	13.3	0.046
Gastric ulcer	1	1.7	2	3.3	9	15.0	0.006
All ulcers	3	5.0	12	20.0	17	28.3	0.003

by the liver and mainly by the kidneys. Gastrin is elevated in serum of patients with Helicobacter pylori (*H pylori*) infection or atrophic gastritis. Few studies have evaluated gastrin levels in cirrhosis, and their contribution towards understanding the pathophysiology of gastric acid secretion is very limited. Avgerinos *et al*[19] evaluated the urinary gastrin output in patients with cirrhosis with and without hepato-renal syndrome. Serum gastrin levels were higher in cirrhotics compared to controls; and in cirrhotics with hepato-renal syndrome the difference was greater suggesting that impaired urinary gastrin secretion may contribute to their hypergastrinemia. The same results were found by Lo *et al*[11] who also showed a significantly lower maximal pepsin output in cirrhotics compared to controls.

Progastrin and gastrin serum levels have been reported to be significantly higher in patients with cirrhosis of any Child-Pugh class compared to controls while there are no differences between controls and patients with chronic hepatitis B or C[20]. Indeed, it is important to note that in this study, the prevalence of *H pylori* infection in cirrhotic patients was 83% *versus* 50% in controls. Therefore, it is not clear whether the difference in progastrin and gastrin level was due to reduced liver metabolism, to *H pylori* infection, or both. In summary, gastrin increase in patients with liver cirrhosis could be related to: (1) impaired hepatic gastrin catabolism; (2) impaired renal function, at least in those with HRS; (3) gastric mucosal alteration due to gastropathy-related cirrhosis.

PEPTIC ULCERS AND LIVER CIRRHOSIS

Many authors reported an increased prevalence of peptic ulcers in patients with cirrhosis[21,22] and it was shown that cirrhotics have an increased risk of developing gastric or duodenal ulcers during an interval of one year compared to non cirrhotics[23]. The prevalence of peptic ulcers ranges between 4.6% and 21% in patients with cirrhosis[21,22,24-26,39] (Table 1). However, the pathogenesis of this finding is far from being elucidated and different factors have been proposed in relation to increased ulcer prevalence in patients with cirrhosis. Furthermore the prevalence of duodenal and gastric ulcers in patients with liver cirrhosis increases with disease progression[27] (Table 2). Several theories have been postulated. It has been demonstrated that the gastric mucosa in rats with portal hypertension is more susceptible to aggressive agents such as bile acids, aspirin and alcohol[28]. Some investigators have attributed to portal hypertension itself the increased risk of peptic ulcer[29], nevertheless no study has clarified the pathogenesis of peptic ulceration in cirrhosis.

H PYLORI IN PATIENTS WITH LIVER CIRRHOSIS

The prevalence of *H pylori* in patients with cirrhosis has been investigated in many epidemiological studies with values ranging from 27% to 89%[24,27,30-33]. This large variability may be due to the test used to evaluate *H pylori* infection. In the study with the largest prevalence of *H pylori* infection, values were been obtained by titration of serum IgG, against *H pylori*. The tests usually used for evaluating the presence of *H pylori* should be revised since haemodynamic alterations in cirrhosis could impair the results of urea 13C BT, and hypergammaglobulinemia typical of cirrhosis, might produce a false positive test[34-38]. Italian studies generally and sometimes significantly showed a higher prevalence than in non cirrhotic patients, while studies from Taiwan failed to show a similar trend. When evaluating the prevalence of *H pylori* infection in cirrhotics there seems to be no relationship between the aetiology of cirrhosis and the prevalence of *H pylori* evaluated by determination of serum IgG[24]. The role of *H pylori* in determining peptic ulceration in cirrhosis is controversial: some authors conclude that the increased risk of gastroduodenal ulcer is not related to *H pylori* infection, whilst others conclude that peptic disease and non-ulcer dyspepsia are firmly linked to *H pylori* infection[32,39-41]. A meta-analysis showed an increased risk of ulcers developing in patients with *H pylori* infection and cirrhosis[42].

If *H pylori* infection were an etiopathological factor implicated in digestive bleeding in cirrhosis, eradication of infection would decrease the risk of ulcer recurrence. However a study aiming to investigate the role of *H pylori* eradication in cirrhotics demonstrated a similar recurrence rate between cirrhotics with successful *H pylori* eradication and those with active *H pylori* infection[43]. In conclusion, the role of *H pylori* infection in the occurrence of gastric or duodenal ulcers or in determining digestive bleeding in the setting of liver cirrhosis is still unclear.

ESOPHAGEAL DISORDERS AND LIVER CIRRHOSIS

It has been postulated in the past, that gastro-esophageal reflux may contribute to oesophagitis and variceal

bleeding in cirrhotic patients[44], and acid reflux could be exacerbated by the presence of ascites and water retention[45]. More recent papers do not confirm these hypotheses[46,47] and report a high incidence of gastro-esophageal reflux only in patients with alcoholic cirrhosis, though the presence of reflux did not correlate with disease severity or bleeding episodes[48]. Functional studies showed decreased lower esophageal sphincter function with low amplitude of primary peristalsis and acid clearance in patients with large varices[49-51]. These phenomenon could also be due to a mechanical effect of the presence of varices. In conclusion, it is unclear whether the presence of cirrhosis itself could predispose to the onset of gastro-esophageal reflux. It seems that the presence of varices is related to reflux episodes, although it is not clear whether these might contribute to bleeding from varices.

Another more studied point is the fact that endoscopic treatment for variceal bleeding or prevention of bleeding varices, may produce oesophageal motility dysfunction. Several studies evaluated the effect of endoscopic variceal sclerotherapy (EVS) on gastro-oesophageal reflux. Some authors suggest that endoscopic treatment produces an acute impairment of oesophageal motility which is partially restored after days or weeks[52-54], others suggest that sclerotherapy produce a chemical esophagitis that impairs oesophageal motility and in turn may favour acid related reflux esophagitis[55]. It seems that endoscopic variceal ligation (EVL) is safer in terms of oesophageal dysmotility induction when compared to EVS[56-59]. The reason for this finding is unclear. Autoptical studies after EVS show the presence of obliteration of the submucosal vascular channels, fibrosis and oesophagitis[60] reflecting the necrosis induced by the sclerosing agent. The inflammation caused by EVS may justify motor dysfunctions and acid reflux. Avgerinos *et al*[61] showed that EVL produces a higher early increase in lower oesophageal sphincter pressure, and this might prevent gastro-oesophageal reflux.

Apart from the pathogenesis of motor dysfunction following EVS and EVL, these procedures are related to local complications such as oesophageal ulcerations, strictures and perforations[62,63]; although from this point of view, EVL seem to be safer than EVS[64,65]. Uncontrolled non randomized studies, showed that PPI may have a role in the prevention and healing of post-EVS ulcerations[66-69] although this was not confirmed by other authors[70]. With regard to post EVL ulcers, the incidence is between 2% to 5%[71,72]. Pantoprazole has been shown to reduce the size of ulcers in patients undergoing elective band ligation, but not the rate of occurrence or the symptoms[73]. Given the relatively benign nature of the intervention, the authors conclude that PPI treatment is advisable in patients undergoing elective EVL.

In summary, expert opinion based on evidence of scarce value, advise PPI use in cirrhotic patients undergoing endoscopic treatment for varices, especially when treatment is performed by EVS, to prevent gastro-esophageal reflux which may worsen the procedure related inflammation or ulceration.

PPI SAFETY IN CIRRHOTIC PATIENTS

Acute hepatitis due to PPI use is described in the literature for most PPIs available on the market[74-79]. All PPIs are metabolized in the liver by cytochrome CYP450; two isoenzymes are involved in PPI metabolism (CYP2C19 and CYP3A4)[6]. CYP2C19 is the main metabolic pathway while CYP3A4 is activated only when the other enzyme is saturated[80]. Nevertheless, the affinity of each isoenzyme for different PPIs is different and rabeprazole is metabolized mainly by a non enzymatic pathway. There are two CYP2C19 phenotypes: extensive and poor metabolisers[81-83]. The poor phenotype is present in 2%-6% of Caucasians and 20% of the Asian population. Poor metabolisers have higher plasma levels of PPI, which could lead to higher efficacy but also to potential adverse events. The effects of these genotypes varies according to the specific PPI used and in general is greater when using omeprazole decreasing progressively to lansoprazole, esomeprazole, pantoprazole and finally rabeprazole[6,83].

PPI are metabolized in the liver and secreted by the kidney. Renal impairment has minimal effect on PPI clearance, and therefore there is no need to reduce PPI dosage in patients with renal diseases[80,84]. This is not the case for liver impairment in which the Area under the Curve (AUC) of PPIs increases and their half-life becomes 4 h to 8 h greater[80] with increasing risk of accumulation. This effect was also seen with rabeprazole[85] although a dose reduction seems to be unnecessary with a 20 mg, once daily dose in patients with mild to moderate liver cirrhosis. When using other PPIs or rabeprazole at 40 mg/d dose, dose reduction in patients with cirrhosis is advisable.

CONCLUSION

PPI drugs are extensively used in clinical practice in cirrhotic patients. Besides habit, the evidence that PPI are necessary in most indications is very weak. First of all, there is convincing evidence that acid secretion is reduced in patients with liver cirrhosis. This is mainly due to the presence of hypertensive gastropathy for which there is no evidence of any efficacy of PPI. With regard to *H pylori* infection, its prevalence in patients with cirrhosis is largely variable among different studies, probably as a result of different diagnostic tests used. We believe that the condition of hypochloridemia of cirrhotics makes it more probable that its prevalence is lower than in the general population. Nevertheless, it seems that *H pylori* eradication does not prevent from gastro-duodenal ulcer formation and bleeding.

It is probable that the main reason for PPI use in cirrhosis might be the prevention and treatment of oesophageal complications after banding or sclerotherapy of oesophageal varices. However even in this case evidence for a protective role of PPI are scarce. When using PPI in cirrhotic patients, the dose should be reduced in consideration of the increased half-life of these drugs in this group of patients. Dose adjustment does not seem necessary when using rabeprazole at a 20 mg, once daily

dose. The use of this class of drugs seems more habit-related than evidence- based, eventually leading to an increase in health costs.

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